REMARKS

Amendments to the Claims

Claims 14-17, 20-27, 30-33, 63, and 65-70

Claims 14-17, 20-27, 30-33, 63, and 65-70 have been cancelled without prejudice to Applicants' right to pursue any subject matter contained therein at a later date in this or another patent application, as Applicants believe that the same is deserving of a patent.

Claim 71

Claim 71 has been amended as follows:

a) The term "relative" has been deleted in response to the Examiner's position that the term renders the claim indefinite. (*See,* the Examiner's 2/26/08 Office Action, at pg. 2).

b) The language referring to identification of "a polymorphic form [of a gene] as associated with a bone density pathology" has been deleted in response to the Examiner's contention this language broadly requires the "possession and enabled use of any and all polymorphic genetic sequences associated with the human gene encoding a vitamin D receptor and a human gene encoding interleukin-6 in context of any kind of undesirable bone condition." (*See*, the Examiner's 2/26/08 Office Action, at pg. 6). The foregoing language has been substituted with language relating to identification of "occurrence in a human's genome of a quantity of [specifically identified and claimed] polymorphisms." A quantity of polymorphisms can be arithmetically summed to yield a value based on observation (or absence) of the claimed

polymorphism(s). Support for this amendment is found throughout the specification as originally filed, specifically including without limitation pg. 8, at ¶22 ("the number of polymorphisms that occur in the human's genome are summed to yield a value; the higher the value is, the greater the susceptibility of the human to an undesirable bone density condition"); pg. 11, at ¶37 ("the degree to which a human is susceptible to an undesirable bone density condition can be assessed by determining which polymorphic forms of certain genes are present in the human's genome"); pg. 15, at ¶46; and pg. 16, at ¶47 ("susceptibility can be calculated relative to a hypothetical human whose genome does not contain a single disorder-associated polymorphism").

i) The Applicants wish to address the Examiner's argument that "[t]he specification fails to disclose any variants of gene encoding vitamin D receptor and interleukin-6 and association thereof with any kind of undesirable bone conditions." (*See*, the Examiner's 2/26/08 Office Action, at pg. 6). The scope of the Applicants' invention is not appreciated. The Applicants' invention addresses the "need for a method of assessing the overall state of bone density regulation in a human and for a method of assessing a person's predisposition to develop an undesirable bone density condition." (*See*, the Specification-as-filed, pg. 4, at ¶4). Identification of a polymorphic form of the VDR gene and/or the IL-6 gene in the manner claimed "is an indication that the gene is aberrant and can contribute to osteopenia

or to another form of an undesirable bone density condition such as osteoporosis or osteopetrosis. (*See*, the Specification-as-Filed, pg. 12, at ¶38; pg. 9, ¶30). In that connection, "[i]t was not previously appreciated that the detection in a human's genome of two or more disorder-associated polymorphisms in genes associated with bone density regulation is indicative that the human globally exhibits enhanced susceptibility to an undesirable bone density condition." (*See*, the Specification-as-filed, pg. 14, at ¶45). This is an important discovery as the Applicants' invention readily determines whether an individual exhibits enhanced susceptibility to (*i.e.*, is at risk of developing) an undesirable bone density condition. Accordingly, appropriate therapeutic and/or preventive measures may be taken in response to assessment of the individual's genome by practicing the Applicants' invention.

c) Matter purportedly not supported by the specification-as-filed has been deleted from this claim. Specifically, "occurrence of a *BsmI* polymorphism in the gene encoding a vitamin D receptor … occurrence of a *ApaI* polymorphism in the gene encoding a vitamin D receptor … [and] occurrence of a *TaqI* polymorphism in the gene encoding a vitamin D receptor" has been deleted. The polymorphisms claimed pursuant to the present amendment are (i) a polymorphism in the VDR gene manifested as change from a cytosine residue to a thymine residue 8 residues upstream of the normal start codon of

the gene encoding vitamin D receptor, whereby the residue is part of an initiation codon and the gene encodes a variant vitamin D receptor comprising three additional amino acids at its amino terminus, and (ii) a polymorphism in the IL-6 gene manifested as a change from a guanine residue to a cytosine residue at position -174 of the interleukin gene 6 promoter. This amendment is fully supported by the specification as originally filed, specifically including without limitation at pg. 15, ¶46 and cancelled claim 33.

d) The claim language relating to assignment a weighting factor to each polymorphism and then summing the weighting factors to yield a value for the human has been deleted (without prejudice to the Applicants' right to claim the same in this or a later application) in response to the Examiner's position that the same is not supported by the specification as filed. (*See*, the Examiner's 2/16/08 Office Action, at pg. 3).

e) The language relating to the "value of a control" has been deleted in response to the Examiner's contention that the same is indefinite. (*See*, the Examiner's 2/26/08 Office Action, at pg. 2). In place of the deleted language, the Applicants claim that "a value for the human greater than zero indicates a greater susceptibility to an undesirable bone density condition for the human." This amendment is fully supported by the specification as originally filed, specifically including without limitation at pg. 16, at ¶47 ("susceptibility can be calculated relative to a hypothetical human whose genome does not contain

a single [*i.e.*, zero] disorder-associated polymorphism"); R.Ricciardi's 11/16/07 Declaration, at ¶17.

Support for the amendments to claim 71 can be found throughout the specification as originally filed, as noted herein above.

In light of the foregoing, no new matter has been added by way of this amendment. Accordingly, claim 71 as amended is now pending.

Claim 72

Claim 72 has been amended such that a "susceptibility value of zero represents an absence of a polymorphic form." Support for amended claim 72 can be found throughout the specification as originally filed, specifically including without limitation on page 16, at ¶47. Thus, no new matter has been added by way of this amendment. Accordingly, claim 72 is now pending.

Claim 73

Claim 73 has been amended to conform the language thereof to amended claim 71. Support for claim 73 can be found throughout the specification as originally filed, specifically including without limitation on pg. 8, at ¶25.

Claim 74

Claim 74 is newly added. Support for claim 74 can be found throughout the specification as originally filed, specifically including without limitation on pg. 4, at ¶¶12-13 (the invention assesses "the overall state of bone density regulation in a human…and predisposition to develop an undesirable bone density condition" by "assessing occurrence in a human's genome of two or more disorder-associated

polymorphisms"); pg. 9, at ¶30; pg. 13, at ¶41 ("Occurrence of disorder-associated polymorphisms…can provide direct **or surrogate** indication of the occurrence of, or risk for development of, and undesirable bone density condition in a human.")(Emphasis added); pg. 14, at ¶45 ("[G]enes which encode enzymes that affect vitamin D metabolism have an important role in bone density regulation. Polymorphisms in these genes can also affect an individual's propensity to develop an undesirable bone density condition"); pg. 15, at ¶46 ("Examples of polymorphisms…which can be informative for assessing susceptibility to an undesirable bone density condition include…a polymorphism manifested as a change from a cytosine to a thymine in the vitamin D receptor (VDR) gene which creates an initiation codon (ATG) three codons proximal to the start site and produces a variant polypeptide comprising three additional amino acids"); pg. 16, at ¶47 ("[S]usceptibility can be calculated relative to a hypothetical human whose genome does not contain a single disorder-associated polymorphism"). Thus, no new matter has been added by way of this amendment. Accordingly, claim 74 is now pending.

Claim 75

Claim 75 is newly added. Support for claim 75 can be found throughout the specification as originally filed, specifically including without limitation on pg. 4, at ¶¶12-13 (the invention assesses "the overall state of bone density regulation in a human…and predisposition to develop an undesirable bone density condition" by "assessing occurrence in a human's genome of two or more disorder-associated polymorphisms"); pg. 9, at ¶30; pg. 13, at ¶41 ("Occurrence of disorder-associated polymorphisms…can provide direct **or surrogate** indication of the occurrence of, or risk

for development of, and undesirable bone density condition in a human.")(Emphasis added); pg. 14, at ¶45 ("[G]enes which encode enzymes that affect vitamin D metabolism have an important role in bone density regulation. Polymorphisms in these genes can also affect an individual's propensity to develop an undesirable bone density condition"); pg. 15, at ¶46 ("Examples of polymorphisms…which can be informative for assessing susceptibility to an undesirable bone density condition include…a polymorphism manifested as a change from a cytosine to a thymine in the vitamin D receptor (VDR) gene which creates an initiation codon (ATG) three codons proximal to the start site and produces a variant polypeptide comprising three additional amino acids"); pg. 16, at ¶47 ("[S]usceptibility can be calculated relative to a hypothetical human whose genome does not contain a single disorder-associated polymorphism"). Additional support for claim 75 is found in the 11/16/07 Declaration of Robert P. Ricciardi, Ph.D. on pg. 5, at ¶21 ("Assessing the relative degree to which a human is susceptible to an undesirable bone density condition…requires determining whether a polymorphism in each of the vitamin D receptor and the IL-6 gene is present"); pg. 6, at ¶24. And, further support for the polymorphisms Applicants claim in a gene encoding a vitamin D receptor and a gene encoding interleukin-6 is found in the prior art; specifically, Ferrari, *et al.*, "A Functional Polymorphic Variant in the Interleukin-6 Gene Promoter Associated with Low Bone Density Resorption in Postmenopausal Women," Arthritis Rheum. 44, 196-201 (2001)(cited in the specification), and Gennari, *et al.*, "Vitamin D and Estrogen Receptor Allelic Variants in Italian Postmenopausal Women: Evidence of Multiple Genes Contributing to Bone Mineral Density," J.Clin.Endocrinol.Metab. 83, 939-944 (1998). A

search of the literature by one of ordinary skill in the art at the time the invention was made would have found the aforementioned references. Finally, cancelled claim 1 supports the amendment. Thus, no new matter has been added by way of this amendment. Accordingly, claim 75 is now pending.

Summary of Now-Pending Claims

In light of the foregoing, Claims 71-75 are now pending in this application following entry of this amendment. Applicant respectfully submits that the now-pending claims are in condition for allowance.

Claim Rejection – 35 U.S.C. § 112, ¶ 2 (Indefiniteness)

The Examiner rejected claims 14-17, 20-27, 30-33, 63 and 65-70 as indefinite under 35 U.S.C. § 112, ¶ 2. This rejection was continued from the Examiner's 7/16/07 Office Action over the Applicants' 11/16/07 Response thereto (including the amendment to the claims further to the Examiner interview of 10/16/07) and the 11/16/07 Declaration of Robert P. Ricciadi, Ph.D. made pursuant to 37 C.F.R. §1.132. (*See,* the Examiner's 2/26/08 Office Action, at pg. 2). While the Applicants maintain that the matter contained in claims 14-17, 20-27, 30-33, 63 and 65-70 particularly point out and claim the subject matter which the Applicants regard as their invention, it is respectfully submitted that the subject claims have been cancelled by the present amendment.

Claim Rejection – 35 U.S.C. § 112, ¶ 1 (New Matter)

The Examiner rejected claims 69-73 (prior to the present amendment thereof) under 35 U.S. C. § 112, ¶ 1 for purportedly introducing new subject matter not described

in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors were in possession of the claimed invention at the time the application was filed. (*See*, the Examiner's 2/26/08 Office Action, at pg. 4). In particular, the Examiner claims that the Applicants failed to "indicate where in the specification as filed there is support" for claims 69-73 prior to the cancellation and/or amendment thereof. (Id.) The Applicants respectfully state that now-pending claims 71-73 are now fully supported by the specification as originally filed and specific reference to the specification is cited herein.

By the present amendment claims 69 and 70 are canceled, claims 71-73 are amended, and claims 74-75 are newly added. Accordingly, as previously stated, claims 71-75 are fully supported by the specification-as-filed as more fully described in herein above.

Claim Rejection – 35 U.S.C. § 112, ¶ 1 (Written Description)

The Examiner rejected claims 14-17, 20-27, 30-33, 63, and 65-73 (prior to the present amendment thereof) under 35 U.S.C. § 112, ¶ 1, as purportedly failing to comply with the written description requirement. As claims 14-17, 20-27, 30-33, 63, and 65-70 have been cancelled without prejudice by the present amendment, this response addresses the Examiner's rejection with respect to claims 71-73 only.

By the present amendment, there are now no genus claims. Accordingly, the Examiner's rejection for insufficient written description relative to a genus claim is rendered moot. (*See*, the Examiner's 2/26/08 Office Action, at pg. 6, *et seq*.).

The Applicants maintain that the claimed invention is now clearly enabled throughout its full scope and supported by the specification as filed. Accordingly, the Applicants request that the rejection be withdrawn.

Without acquiescing in the present grounds for rejection, by this amendment and the remarks contained herein, Applicants believe that the Examiner's present grounds for rejection have been obviated and respectfully request reconsideration and withdrawal of the present rejection under 35 U.S.C. §112, ¶¶1-2.

No Disclaimers or Disavowals Are Contained Herein

Although the present communication may include alterations to the application or claims, or characterizations of the claim scope or referenced art, the Applicants do not concede in this application that the previously pending claims are not patentable over the cited references. Rather, any alterations or characterizations are being made merely to facilitate expeditious prosecution of this application. The Applicants reserve the right to pursue at a later date any of the previously pending or other broader or narrower claims that capture any subject matter supported by the present disclosure, including subject matter found to be specifically disclaimed herein or by any prior prosecution. Accordingly, reviewers of this or any parent, child, or related prosecution history shall not reasonably infer that the Applicants have made any disclaimers or disavowals of any subject matter supported by the present application.

Conclusion

It is respectfully submitted that each of the presently pending claims (71-75) is in condition for allowance and notification to that effect is requested. Further, Applicants

respectfully submit that each of the outstanding rejections have been addressed herein and resolved such that the pending claims are in condition for allowance.

The undersigned has made a good faith effort to respond to and overcome all of the rejections in this case and to place the claims in condition for immediate allowance. Nevertheless, if any undeveloped issues remain or if any issues require clarification, the Examiner is invited to contact Applicants' undersigned representative if it is believed that prosecution of this application may be assisted thereby. Although only certain arguments regarding patentability are set forth herein, there may be other arguments and reasons why the claimed invention in patentable. Applicants reserve the right to raise these arguments in the future.

The fees believed to be due, if any, have been paid at the time of filing this communication.

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Respectfully submitted,
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MARKED-UP COPY OF THE CLAIMS AS AMENDED
(Provided for the Examiner's convenience only)

1 – 70. (Canceled)

71. (Currently Amended) A method comprising

assessing ~~a relative~~ the degree to which a human is susceptible to an undesirable bone density condition by identifying ~~a polymorphic form identified as associated with a bone density pathology in each of~~ occurrence in a human's genome of a quantity of polymorphisms in each of two genes, the genes consisting of

a gene encoding a vitamin D receptor (VDR) present in the human's genome, and

a gene encoding interleukin-6 (IL-6) present in the human's genome

~~wherein the polymorphic form is selected from the group consisting of~~

~~a) occurrence of a *FokI* polymorphism in the gene encoding a vitamin D receptor defined by a C/T nucleotide in exon 2, at the first of two potential translation sites, whereby the residue is part of an initiation codon and the gene encodes a variant vitamin D receptor comprising three additional amino acids at its amino terminus;~~

~~b) occurrence of a *BsmI* polymorphism in the gene encoding vitamin D receptor defined by a T/C change in intron 8;~~

~~c) occurrence of a *ApaI* polymorphism in the gene encoding vitamin D receptor defined by a T/G change in intron 8;~~

~~d) occurrence of a *TaqI* polymorphism in the gene encoding vitamin D receptor defined by a T/C change in exon 9; and~~

~~e) occurrence of a polymorphism in the IL-6 gene promoter defined by a G/C change at position -174,~~

wherein the polymorphism in the VDR gene is a polymorphism manifested as change from a cytosine residue to a thymine residue 8 residues upstream of the normal start codon of the gene encoding vitamin D receptor, whereby the residue is part of an initiation codon and the gene encodes a variant vitamin D receptor comprising three additional amino acids at its amino terminus, and the polymorphism in the IL-6 gene is manifested as a change from a guanine residue to a cytosine residue at position -174 of the interleukin gene 6 promoter

thereafter calculating a susceptibility value for the condition by ~~either~~

summing the quantity of identified polymorphisms to yield a value for the human~~, or~~

~~assigning a weighting factor to each polymorphism and then summing the weighting factors to yield a value for the human,~~

wherein a value for the human greater than ~~a value for a control~~ zero indicates a greater susceptibility to ~~the~~ an undesirable bone density condition for the human~~,~~, ~~and wherein the polymorphic form is a disorder associated polymorphism,~~

~~the method hereby assessing the relative degree to which the human is susceptible to the undesirable bone density condition.~~

72. (Currently Amended) The method of claim 71 wherein the susceptibility value ~~for the control is~~ of zero ~~and~~ represents an absence of a polymorphic form identified as associated with a bone density pathology in each of a gene encoding a vitamin D receptor present in the human's genome and a gene encoding interleukin-6 present in the human's genome.

73. (Currently Amended) The method of claim 71 wherein the ~~polymorphic form~~ polymorphism is a single nucleotide polymorphism (SNP).

74. (New) A method comprising assessing occurrence in a human's genome of polymorphisms in each of two genes, the genes consisting of a gene encoding a vitamin D receptor (VDR) and a gene encoding interleukin-6 (IL-6),

wherein the polymorphism in the VDR gene is a polymorphism manifested as change from a cytosine residue to a thymine residue 8 residues upstream of the normal start codon of the gene encoding vitamin D receptor, whereby the residue is part of an initiation codon and the gene encodes a variant vitamin D receptor comprising three additional amino acids at its amino terminus, and the polymorphism in the IL-6 gene is manifested as a change from a guanine residue to a cytosine residue at position -174 of the interleukin gene 6 promoter;

whereby occurrence of the polymorphic form in each gene indicates an increased susceptibility of the human to an undesirable bone density condition relative to a human with fewer or no occurrences of the polymorphic form.

75. (New) A method comprising assessing occurrence in a human's genome of polymorphisms in each of two genes, the genes consisting of a gene encoding interleukin-6 (IL-6) and a gene encoding a vitamin D receptor (VDR),

wherein the polymorphism in the IL-6 gene is manifested as a change from a guanine residue to a cytosine residue at position -174 of the IL-6 promoter and the polymorphism in the VDR gene is selected from the group consisting of:

a) a polymorphism manifested as change from a cytosine residue to a thymine residue 8 residues upstream of the normal start codon of the gene encoding vitamin D receptor, whereby the residue is part of an initiation codon and the gene encodes a variant vitamin D receptor comprising three additional amino acids at its amino terminus; and

b) a *FokI* polymorphism defined by a C/T nucleotide in exon 2, at the first of two potential translation sites, whereby the residue is part of an initiation codon and the gene encodes a variant vitamin D receptor comprising three additional amino acids at its amino terminus;

whereby occurrence of the polymorphic form in each gene indicates an increased susceptibility of the human to an undesirable bone density condition relative to a human with fewer or no occurrences of the polymorphic form.